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APPLICATION NO.	FILING DATE	MILLER	FIRST NAMED INVENTOR	20161/0425	ATTORNEY DOCKET NO.
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IM62/0425

EINSMANN, JR.
EXAMINER

1/21 ART UNIT PAPER NUMBER

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ANDREA DECECCHIS
DOCKET COORDINATOR
PATENT DEPARTMENT

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 37

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Application Number: 08/801,327
Filing Date: February 18, 1997
Appellant(s): Bernhard Muller

MAY 1 2000

ANDREA DECECCHIS
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PATENT DEPARTMENT

MAILED

APR 25 2000

GROUP 1700

Kevin T. Mansfield
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed February 28, 2000.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

DOCKETED

FOR: June 25, 2000
Req. for Oral Hearing / Reply Brief

1-20161 / A / CONT / CPA 4

Art Unit: 1751

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) *Summary of Invention*

The summary of invention contained in the brief is correct.

(6) *Issues*

The appellant's statement of the issues in the brief is correct.

(7) *Grouping of Claims*

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because applicant has not provided arguments why claims 8-10 and 19 are separately patentable except for the fact that they are of narrower scope than claims 2-3, 5-7 and 16-18. M.P.E.P. 1.192 (c) (7) states that merely pointing out differences in what the claims cover is not an argument as to why the claims are separately patentable.

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(8) *Claims Appealed*

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) *Prior Art of Record*

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

GB 2,034,731

Harms et al.

June 11, 1980

(10) *Grounds of Rejection*

The following ground(s) of rejection are applicable to the appealed claims:

Claims 2-3,5-10,16-19 are rejected under 35 U.S.C. § 103 as being unpatentable over Harms et al., GB 2,034,731.

Harms discloses water soluble reactive dyestuffs inclusive of applicant's dyestuff 1 when they contain the selected alkyl radicals as the B₁ aliphatic bridge member. Harms teaches that such bridge may be a straight or branch chain alkylene having 2-15 carbon atoms. See page 1 especially line 29 to page 2 line 5. Applicant claims three embodiments of the B₁ bridge member, two of which are five carbon, pentane isomers, and the third being a three carbon alkyl substituted by hydroxy. While Harms et al. does not suggest the hydroxy substituted bridging group, they specifically disclose four five carbon isomers as bridging groups on page 1 lines 34 and 35. Note that the preferred bridge member of applicant's

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claims 8,9 and 19 is specifically listed among the five carbon bridge member on line 35 of page 1.

Harms differs from applicant's formula 1 in failing to show a working example of the five carbon isomers as claimed herein for the B₁ component in the instantly claimed dyestuffs.

The subject matter would have been obvious to the skilled artisan absent a showing of criticality because it is clear from the examples of bridge members exemplified in the disclosure from page 1 lines 32 to page 2 that five carbon alkyl isomers included as embodiments of the alkyl bridge member. The bridge member of claim 19 as disclosed on page 1 of Harms is thus equivalent to the aliphatic bridge members of the working examples. Additionally, note that structurally similar compounds are generally expected to have similar properties. *In re Gyurik*, 596 F. 2d 1012, 201 USPQ 552. Closely related homologs, analogs and isomers in chemistry may create a prima facie case of obviousness. *In re Dillon* USPQ 2d 1897, 1904 (Fed. Cir. 1990); *In re Payne* 203 USPQ 245 (CCPA 1979); *In re Mills* 126 USPQ 513 (CCPA 1960); *In re Henze* 85 USPQ 261 (CCPA 1950); *In re Hass* 60 USPQ 544 (CCPA 1944).

(11) Response to Argument

Appellant does not dispute that the five carbon isomeric bridge members claimed would have been obvious absent a show of criticality. (page 5 fourth paragraph of brief). Appellant states that the Declaration of Dr. Muller dated August 22, 1996 demonstrates that the dye according to the present application has a distinctly better buildup, and hence better affinity to

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cotton fiber material, and that said improvement was very surprising and of commercial importance, and he would not have predicted it. The examiner's position is that the declaration did not compare the closest prior art compound since the compound compared has a three carbon bridge and there are several examples which were closer to the claimed compound, in particular, the dyes of examples 48 and 74, both of which have a five carbon bridge, which is an isomer of the two carbon bridges in the claimed dyes. Appellant states that the specification does not teach a method of making the intermediate, 2,4-diaminopentane, which is necessary to form the bridge of those two dyes. Appellant states that 2,4-diaminopentane is not available that it could not be synthesized. He presented a declaration dated July 7, 1999 in which he described two synthetic methods which were tried and did not result in 2,4-diaminopentane being formed. Since the intermediate could not be made, appellant argues that the teaching of Harms fails to satisfy the enablement requirement with regard to the dyes of examples 48 and 74. Since no significant properties are listed for the dyes of examples 48 and 74, the dyes are merely prophetic. One skilled in the art was not enabled to make an use those dyes. Appellant has cited case law which substantiates his position that when no method exists for the preparation of a compound, the mere naming of a compound cannot constitute a description of said compound. In response to this argument, the examiner states that the specification gives the synthesis of the class of dyes on page three line 6 et seq. A specific example of the synthesis is example 73 on page 17. In order to obtain compound IV on page 3 to form dye 48 or 74, appellant states that he needs 2,4-diaminopentane. The

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examiner disputes the statement that said compound was not available or could not be made by one having ordinary skill in the art, an organic chemist, at the time the invention was made by pointing to the description of the synthesis of 1,3-dimethyl-1,3-diaminopropane and the listing of its physical properties in the article by Buxtorf et al in Helvetica Chemica Acta, Vol 57, 1974, page 1035.(see Appendix). Thus the specific dyes of Harms et al. are enabled.

Additionally, appellant argues that the dye of Harms used in the comparison in the Mueller declaration of 8/22/96 has a three carbon chain between the aromatic rings, with one methyl on one of the nitrogens and hence the comparison is closer than it at first appears. The response to that argument is that:

1. The closest compounds, 48 and 74, have not been compared.
2. When appellant averred that said compounds could not be made, no attempt was made to compare any of the exemplified dyes having four or six carbon bridges with the inventive dyes.

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For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Margaret Einsmann

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April 24, 2000

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112. Metal Complexes with Macrocyclic Ligands, IV¹⁾. Synthesis, Properties and Kinetics of Complexation with Three N-methyl Substituted 1,4,8,11-tetraazacyclotetradecanes

by Rudolf Buxtorf and Thomas A. Kaden

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(20. II. 74)

Summary. The synthesis, properties and complexation of 1-methyl-1,4,8,11-tetraazacyclotetradecane (1-MeCyclam-14), 1,5-dimethyl-1,5,8,12-tetraazacyclotetradecane (2-MeCyclam-14) and 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (4-MeCyclam-14) are described.

While the Ni²⁺ and Cu²⁺ complexes of 1-MeCyclam-14 and 2-MeCyclam-14 exhibit square planar geometries, 4-MeCyclam-14 forms Ni²⁺ and Cu²⁺ complexes, whose absorption spectra are best explained by assuming pentaco-ordination of the metal ions.

The complexation rate of the three N-methyl substituted macrocycles with Cu²⁺ and Ni²⁺ is slower than can be accounted for by water exchange and little affected by introducing methyl groups at the nitrogens. Both results are in contrast to what is known for open chain amine ligands. A mechanism for the complexation is proposed, which also explains why the products of the reaction of 4-MeCyclam-14 with Cu²⁺ and Ni²⁺ are pentaco-ordinated.

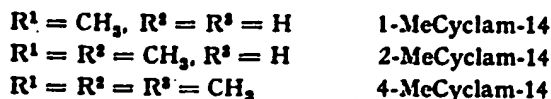
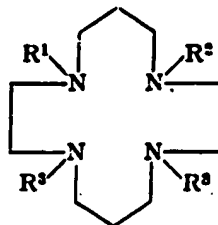
The complexation rate of transition metal ions with macrocyclic ligands is much slower than with analogous open chain compounds [2-4]. Based on such comparisons it has been concluded that the rate determining step of the complex formation with tetraazacyclotetradecanes is not the dissociation of the first co-ordinated water molecule [2-4]. In the meantime Rorabacher *et al.* [5] have shown that N-substitution strongly affects the complexation rate of open chain amines with Ni²⁺ raising the question whether the observed slow reaction with macrocyclic ligands could similarly be explained.

The present investigation was undertaken with a twofold aim. For one we wanted to study systematically the effects of N-methyl substitution on the complexation rate of tetraazacyclotetradecanes, secondly we hoped to prove the hypothesis, that the conjugate base of the pentaco-ordinated [6] blue intermediate plays an important role in the complexation of *meso*-5,7,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane (tet a or 1,7-CTH) with Cu²⁺ [3]. Replacement of all the hydrogen atoms of the four amino groups of the ligand by methyl groups should prevent the forma-

¹⁾ Part III, see [1].

tion of the conjugate base as well as the interconversion of the pentaco-ordinated into the square planar structure.

For these purposes we have synthesized the following three N-methyl substituted macrocycles:



Experimental Part. - N,N'-Ditosyl-N,N'-diacetic acid (I) was synthesized according to the literature [7], with the only difference that ethylbromoacetate instead of methylbromoacetate was used. Yield and properties of the product were similar to those described.

1,3-Dimethyl-1,3-ditosyl-1,3-diaminopropane (II). 100 g 1,3-ditosyl-1,3-diaminopropane disodium salt and 77 g methyl iodide were reacted in boiling abs. MeOH. The solvent was evaporated and the resulting oil shaken with 200 ml of water and 400 ml of CHCl_3 . The CHCl_3 phase was twice extracted with 200 ml of water, dried over Na_2SO_4 and evaporated. The residue was crystallized from MeOH and gave 65 g (61%) of white crystals (II), m.p. 110–111° (113° [8]).

1,3-Dimethyl-1,3-diaminopropane (III). 97.2 g of II were hydrolyzed with 80% H_2SO_4 during 6 h at 120°. A concentrated solution of NaOH was added until pH > 12 and the amine separated by steam distillation. After extraction with ether the compound was distilled over sodium yielding 15 g (62%) of III, b.p. 142–145° (142° [8]). III. 2HCl m.p. 255–258° (266° [8]).

General cyclization procedure. The cyclization was accomplished according to the procedure of Stetter & Mayer [7] in a 4 l three necked flask equipped with a stirrer and two 500 ml dropping funnels, with which a constant dropping rate could be maintained. The two cyclization components, a solution of freshly prepared N,N'-ditosyltrimethylenediamine-diacetylchloride in benzene and a solution of two equivalents of the freshly distilled diamine, also in benzene, were slowly added at the same dropping rate within 15–20 h to 1.5 l of abs. benzene. The crude cyclic diamides, which precipitated during the reaction, were isolated after distilling off the solvent and extracting the residue with hot water to dissolve the diaminedihydrochloride formed.

General reduction procedure. The cyclic diamide dissolved in abs. THF was added under stirring to a suspension of 100% excess of LiAlH_4 in 400 ml of refluxing abs. THF during 24–60 h. At the end of the reaction the excess of LiAlH_4 was decomposed by adding water. The precipitated $\text{Al}(\text{OH})_3$ was filtered and extracted in a Soxhlet with THF during 48 h. Evaporation of the combined solutions gave the cyclic amines as brown oils.

1-Methyl-4,8-ditosyl-1,4,8,11-tetraaza-2,10-dioxo-cyclotetradecane (IV). The acid chloride prepared from 15 g of I and SOCl_2 was cyclized with 5.3 g 1-methyl-1,3-diaminopropane (Fluka). The product was crystallized from methanol until thin layer chromatography ($\text{H}_2\text{O}/\text{CH}_3\text{COOH}/\text{butanol}$ 3:1:2, $R_f = 0.7$) showed that it was pure. Yield 10 g (60%), m.p. 207–209°.

$\text{C}_{25}\text{H}_{44}\text{N}_4\text{O}_4\text{S}_2$ Calc. C 54.53 H 6.22 N 10.17% Found C 54.4 H 6.3 N 10.0%

1-Methyl-1,4,8,11-tetraazacyclotetradecane (1-MeCyclam-14). Reduction of 5.5 g of IV in 100 ml abs. THF according to the procedure given above with 2.0 g LiAlH_4 produced an oil, which upon treatment with alcoholic HCl gave a crystalline hydrochloride. Recrystallization from MeOH/ H_2O gave 1.4 g (35%) of the monohydrate of 1-MeCyclam-14. $(\text{HCl})_4$, dec. 220°.

$\text{C}_{11}\text{H}_{20}\text{Cl}_4\text{N}_4 \cdot \text{H}_2\text{O}$ Calc. C 34.95 H 8.53 N 14.80 Cl 37.45%
Found .. 35.12 .. 8.55 .. 14.85 .. 37.52%